10/509823

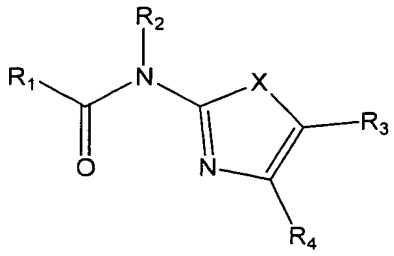
DT04 Rec'd PCT/PTO 30 SEP 2004

1. The last paragraph of page 3 of the description was rewrote, and the "comma" between the two structures in the last line was revised to "or";
2. The first to fourth paragraph of page 4 of the description was rewrote;
3. The page 3 of the description was replaced by the revised page 3/1, 3/2;
4. The page 4 of the description was replaced by the revised page 4/1, 4/2;
5. Claims 1 to 4 were rewrote;
6. In claims 6-10, the " as defined in claim 4" was revised to " as defined in claim 5";
7. In claim 11, the " anti-infection lead compounds" was revised to "" anti-infection drugs";
8. Claims 1-4, 6-11 were replaced by the same numbered revised claims, Claim 5 was not revised; Page 14 was replaced by the revised page 14/1, 14/2; Page 15 was replaced by the revised page 15;

Claims

What is claimed is:

1. A methionine aminopeptidase inhibitor represented by the general formular



wherein

R_1 is selected from the group consisting of

(1) C_1-C_4 alkyl,

(2) C_3-C_6 cycloalkyl,

(3) Aryl,

(4) 2-, 3- or 4- pyridyl,

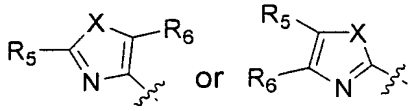
where (1) and (2) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (3) and (4) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio,

and

(5) heterocycle having the following structure:



where R_5, R_6 are selected independently from the group consisting of

(a) hydrogen,

(b) C_1-C_4 alkyl

(c) C_3-C_6 cycloalkyl,

(d) Aryl,

(e) 2-, 3- or 4- pyridyl,

where (b) and (c) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (d) and (e) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio,

X is selected from the group consisting of O、S、N;

R_2 is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_4 alkyl,

(3) C_3-C_6 cycloalkyl,

(4) Aryl,

where (2) and (3) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (4) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) halogen atoms,

(3) C_1-C_4 alkyl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

(4) Aryl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio;

R_4 is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_4 alkyl, which can be optionally substituted with 1, 2, or 3 substituents

independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

(3) Aryl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, carbonylamide, alkylthio, methylthio, ethylthio;

X is selected from the group consisting of O、S、N.

2. A methionine aminopeptidase inhibitor according to claim 1 in which

R_1 is selected from the group consisting of 2-, 3- or 4- pyridyl, each can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, halogen atoms, nitro, carboxyl, aldehyde, alkoxy, alkoxycarbonyl, alkylamino, acylamide;

R_2 is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_6 alkyl,

(3) C_2-C_6 alkenyl,

(4) C_2-C_6 alkynyl,

(5) C_3-C_6 cycloalkyl

(6) Aryl,

(7) benzyl

where (2) and (5) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (6) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, carbonylamide, alkylthio;

R_3 is selected from the group consisting of hydrogen, Br, C_1-C_4 alkyl;

R_4 is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_4 alkyl,

(3) Aryl,

where (3) can be optionally substituted with 1, 2, or 3 substituents independently

selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, carbonylamide, alkylthio;

3. A methionine aminopeptidase inhibitor according to claim 1 in which

R_1 is selected from the group consisting of aryl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of nitro, alkylamino, halogen atoms, C_1-C_4 alkoxy, hydroxy, carboxyl, benzyl;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 alkyl;

R_3 is selected from the group consisting of hydrogen, halogen atoms, C_1-C_4 alkyl;

R_4 is selected from the group consisting of

(1) hydrogen,

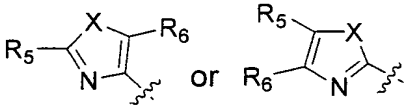
(2) C_1-C_4 alkyl,

(3) Aryl,

where (3) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, halogen atoms, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio;

4. A methionine aminopeptidase inhibitor according to claim 1 in which

R_1 is selected from the following heterocycle structure:



X is selected from the group consisting of O、S、NH;

R_2 is selected from the group consisting of hydrogen, C_1-C_4 alkyl;

R_3 is hydrogen;

R_4 is hydrogen;

R_5, R_6 are selected independently from the group consisting of

(a) hydrogen,

(b) C_1-C_4 alkyl,

(c) C_3-C_6 cycloalkyl,

(d) Aryl,

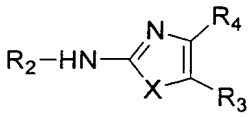
(e) 2-, 3- or 4- pyridyl,

where (b) and (c) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (d) and (e) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio,

5. A process for the preparation of a methionine aminopeptidase inhibitor as defined in claim 1 which comprises condensating of a compound of the general formula R1COY with a compound of the general formula



in which Y represents hydroxyl, halogen atoms and the other activated group;

6. A process for the preparation of a methionine aminopeptidase inhibitor as defined in claim 5 wherein the dehydration reagents used in this reaction may be DCC、ECD、DIC、HBTU;

7. A process for the preparation of a methionine aminopeptidase inhibitor as defined in claim 5 wherein the solvent used in this condensation reaction may be CH_2Cl_2, DMF, CH_2ClCH_2Cl, toluene, benzene, H_2O, dioxane or the mixture of the above solvents;

8. A process for the preparation of a methionine aminopeptidase inhibitor as defined in claim 5 wherein the reaction temperature is from -20°C to room temperature, in some cases, the heating is necessary, from 50° C to 130°C;

9. A process for the preparation of a methionine aminopeptidase inhibitor as defined in claim 5 wherein the proper activated reagents of the condensation reaction were used, such as, HOBT、pentafluorophenol, molecular series;

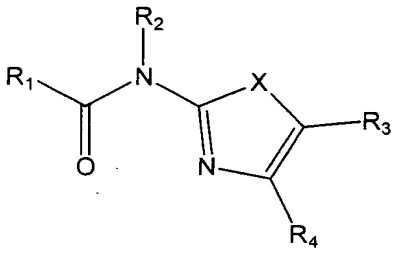
10. A process for the preparation of a methionine aminopeptidase inhibitor as defined in claim 5 wherein the proper base of the condensation reaction such as Et_3N, I-Pr_2EtN, Pyridine, DMAP were used as catalyst;

11. A methionine aminopeptidase inhibitor as claimed in claim 1, wherein these compounds were used as antitumor, and anti-infection drugs.

Aim of the invention: The invention provides a series of small molecular methionine aminopeptidase inhibitors with a novel structure and their structure-activity relationship. These compounds may be used to reveal the function of MetAPs in physiologica and pathologicall conditions, and also used as antitumor, antibacterial and anti-infection lead compounds.

The invention also provides the preparation of these methionine aminopeptidase inhibitors.

In its principle embodiment, the present invention provides a new type of methionine aminopeptidase inhibitors having the generalized structure:



wherein

R_1 is selected from the group consisting of

(1) C_1-C_4 alkyl,

(2) C_3-C_6 cycloalkyl,

(3) Aryl,

(4) 2-, 3- or 4- pyridyl,

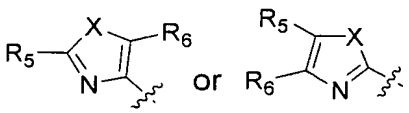
where (1) and (2) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (3) and (4) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio,

and

(5) heterocycle having the following structure:



where R_5, R_6 are selected independently from the group consisting of

(a) hydrogen,

(b) C_1-C_4 alkyl

(c) C_3-C_6 cycloalkyl,

(d) Aryl,

(e) 2-, 3- or 4- pyridyl,

where (b) and (c) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (d) and (e) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio,

X is selected from the group consisting of O、S、N;

R_2 is selected from the group consisting of

(1) hydrogen,

(2) C_1-C_4 alkyl,

(3) C_3-C_6 cycloalkyl,

(4) Aryl,

where (2) and (3) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

and

where (4) can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) halogen atoms,

(3) C_1-C_4 alkyl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

(4) Aryl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, alkylthio;

completed, the mixture was generally extracted with EtOAc, CH_2Cl_2 or $CHCl_3$. After the mixture was washed with 5% aqueous HCl, water and saturated aqueous NaCl, the combined organic phases were dried, and then concentrated under reduced pressure at low temperature and chromatographed to give the desired compound III. The reaction yield is changed according to the properties of reactants I and II, from 20% to 95%, and the obtained products were proved by NMR etc.

Compound II was made as reported in J. Org. Chem. 63, 196-200 (1998).

R_4 is selected from the group consisting of

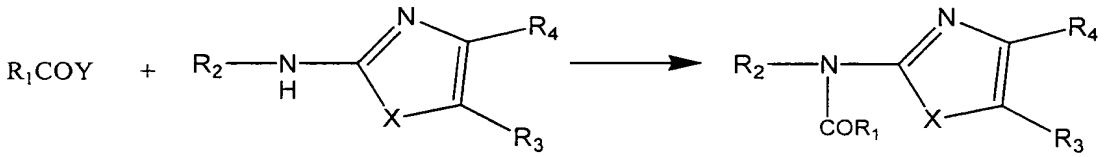
(1) hydrogen,

(2) C_1-C_4 alkyl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halogen atoms, C_1-C_6 alkoxy or hydroxy,

(3) Aryl, which can be optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of C_1-C_4 alkyl, nitro, carboxyl, aldehyde, alkoxy, alkylamino, acylamide, carbonylamide, alkylthio, methylthio, ethylthio;

X is selected from the group consisting of O、S、N.

The invention also provides the preparation of these methionine aminopeptidase inhibitors as the following formula:



I II III

The syntheses of compounds III could be accomplished by the well-precedented condensation of compound I (wherein Y is selected from OH, Cl or other activated group) with compound II, the solvent used in this reaction may be CH_2Cl_2, DMF, CH_2ClCH_2Cl, toluene, benzene, H_2O, dioxane or the mixed solvent when needed such as CH_2Cl_2/DMF (1:1 V/V). The dehydration reagents used in this reaction may be DCC、ECD、DIC、HBTU according to the properties of the compounds, in some cases, the proper activated reagents were used, such as HOBT, pentafluorophenol, molecular sieves, in some cases, the proper base such as Et_3N, I-Pr_2EtN, Pyridine, DMAP were used as catalysts, the reaction temperature is from -20°C to room temperature, in some cases, heating is necessary, from 50° C to 130°C. The reaction time is determined by the activated group of the reactants, when Y is Cl, the reaction is over in minutes, and some reactions need longer time, usually TLC monitoring was used to determine the process of the reaction. When the reaction is